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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/331,375	12/03/1999	CHARLES M. COHEN	CIBT-P01-519	1578

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EXAMINER

DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 10/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Application No.

09/331,375

Applicant(s)

COHEN ET AL.

Examiner

Regina M. DeBerry

Art Unit

1647

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
  - (b) ☐ they raise the issue of new matter (see Note below);
  - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
  - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_.

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 1,5-17,19,20,24,28 and 29.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☒ Other: claims 2-4, 18, 21-23, 25-27 and 30 were canceled.

Claims 1, 5-20, 24, 28 and 29 stand rejected under 35 U.S.C. 112, first paragraph, enablement. The basis for this rejection is set forth at pages 2-8 of the previous Office Action (03 June 2003).

Applicants submit that simply because something has never been shown or done before by another does not necessarily mean that the art is unpredictable. Applicants contend that the reason why no one has done something similar or identical before is because the claimed invention is novel and unobvious, not because the art is so unpredictable that no one can do it. Applicants state that the inventor's theory or belief as to how his invention works is not a necessary element to satisfy the enablement requirement. Applicants cite case law. Applicants need not describe any detailed mechanism behind the invention to enable to the claimed invention. As long as Applicants have provided enough details as how to make and use the claimed invention, the enablement requirement is met. Applicants cite page 12, lines 10-14 to demonstrate that at least one morphogen has been shown to promote differentiation of precursors into functional myocardium.

Applicants' arguments have been fully considered but not deemed persuasive. Contrary to Applicants' assertion, the instant specification fails to teach how to make and use as was stated in the previous Office Action. Page 12, lines 10-14 of the specification does not disclose an experiment demonstrating that at least one morphogen has been shown to promote the differentiation of precursor cells into functional myocardium. The section cited by Applicants discloses prophetic teachings. Applicants submitted a post-filing reference (Behfar) in the previous Office Action to prove that the claimed invention, if practiced as taught in the instant specification, would work. In the last Office Action, the Examiner used the Behfar reference to specifically point out the weaknesses in the instant specification. For example, the Examiner pointed out that the specification, as originally filed does not teach the use of leukemia inhibitory factor (LIF) or any other factor as suppressors of differentiation. The Examiner stated that the specification as originally filed fails to disclose and/or teach specific assays, materials, methods, etc. needed for the invention to be enabled. In addition, the Behfar reference and the instant specification, both fail to teach the use of skeletal muscle satellite cells, or the actual treatment of myogenic precursor cells with a morphogen before, during, or after implantation into a mammal and the use of osteogenic proteins or fragments of osteogenic or bone morphogenic proteins as morphogens to treat the myogenic precursor cells. The Examiner concluded that the subject matter sought to be patented as defined by the claims, is not supported by an enabling disclosure.

Applicants maintain that LIF was cloned in the late 1980's and was known before the earliest priority date of the instant application as having a differentiation inhibitory activity in embryonic stem cells. Applicants state that the instant specification refers to LIF as having this inhibitory effect. Applicants maintain that no matter how LIF is used, the final conclusion of the Behfar experiments is that BMP-2 and other related morphogens, plus TGF-beta) can stimulate ES cell differentiation into functional myocardium. Applicants assert that the specification need not teach the use of LIF or the hanging drop differentiation method, since its immaterial to the invention sought to be patented.

Applicants' arguments have been considered but not found persuasive. The instant specification does not specifically teach the use of any suppressor of differentiation. The instant specification does not disclose LIF as having differentiation inhibitory activity as claimed by Applicants. One skilled in the art would need some sort of suppressor to inhibit premature differentiation. Applicants stated, "TGF-B is not a morphogen of the claimed invention" (15 October 2002, Paper No. 16, page 9). The Examiner pointed out in the previous Office Action that Behfar teaches in vitro cardiac differentiation of stem cells grafted onto cardiomyocytes enhanced by TGF-B and BMP2. Applicants now state that TGF-beta possess the ability to promote myocardium formation.

Applicants submit that teaching a skilled artisan how to verify whether the precursor cells have become myocardium is not required to enable the claimed invention, since this is not one of the steps of the claimed invention and is thus unnecessary for a skilled artisan to practice the invention. Applicants submit that the heart produces certain BMP proteins, thus even without externally administered BMP proteins, the implanted precursor cells will be stimulated by these BMP proteins of endocrine origin to differentiate into functional cardiac muscle. It is expected that externally administered BMPs will enhance this process.

Applicants' arguments have been considered but not found persuasive. The instant claims are drawn to promoting differentiation of myogenic precursor cells into functional myocardium. One would need to discern if the phenotype of the precursor cell has changed to myocardium. Applicants discuss more experiments of Behfar. Applicants state that Behfar teaches that precursor cells implanted in vivo into damaged heart tissue will differentiate into functional myocardium in a BMP-signaling-dependent fashion, even in the absence of externally administered BMPs. Applicants discuss other references which do not appear to be on the IDS of record (Zimmerman et al. and Wada et al.). Applicants arguments are not found persuasive because the specification as originally filed does not teach how to make or use the instant invention. The Examiner has already discussed what the instant specification fails to teach when compared to Behfar. If one skilled in the art can readily anticipate the effect, then there is predictability in the art. In this case, the art is unpredictable. The evidence for the degree of predictability in the art also relates to the amount of direction needed in the specification. The existence of working examples need not contain an example of the invention if disclosed in a manner where one skilled in the art could practice it without undue experimentation. The specification as originally filed, fails to disclose specific direction to make and use the instant invention.

  
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